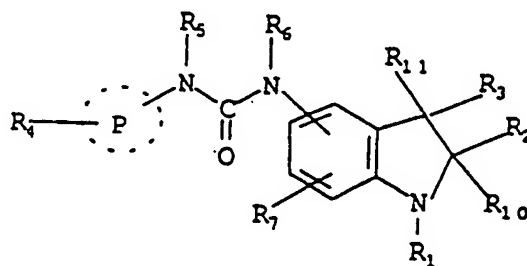


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(21) International Application Number: PCT/GB93/00449 (22) International Filing Date: 4 March 1993 (04.03.93) (30) Priority data: <table border="0"> <tr> <td>9205415.4</td> <td>12 March 1992 (12.03.92)</td> <td>GB</td> </tr> <tr> <td>9205416.2</td> <td>12 March 1992 (12.03.92)</td> <td>GB</td> </tr> <tr> <td>9205422.0</td> <td>12 March 1992 (12.03.92)</td> <td>GB</td> </tr> <tr> <td>9205442.8</td> <td>12 March 1992 (12.03.92)</td> <td>GB</td> </tr> </table> (71) Applicant (for all designated States except US): SMITH-KLINE BEECHAM PLC [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB). (72) Inventors; and (75) Inventors/Applicants (for US only) : FORBES, Ian, Thomson [GB/GB]; MARTIN, Roger, Thomas [GB/GB]; JONES, Graham, Elgin [GB/GB]; Smithkline Beecham Pharmaceuticals, Coldharbour Road, The Pinnacles, Harlow, Essex CM19 5AD (GB).		9205415.4	12 March 1992 (12.03.92)	GB	9205416.2	12 March 1992 (12.03.92)	GB	9205422.0	12 March 1992 (12.03.92)	GB	9205442.8	12 March 1992 (12.03.92)	GB	(74) Agent: GIDDINGS, Peter, J.; Corporate Patents, Smith-Kline Beecham, Mundells, Welwyn Garden City, Hertfordshire AL7 1EY (GB). (81) Designated States: AU, CA, JP, KR, NZ, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i>
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(54) Title: INDOLE DERIVATIVES AS 5HT_{1C} ANTAGONISTS



(I)

(57) Abstract

A compound of formula (I) or a salt thereof wherein P represents a quinoline or isoquinoline residue or a 5- or 6-membered aromatic heterocyclic ring containing up to three heteroatoms selected from nitrogen, oxygen or sulphur; R₁ is hydrogen or C₁₋₆ alkyl; R₂, R₃, R₁₀ and R₁₁ are independently hydrogen or C₁₋₆ alkyl, or R₁₀ and R₁₁ together form a bond, or R₂ and R₁₀ or R₃ and R₁₁ together form a C₂₋₆ alkylene chain; R₄ is hydrogen, C₁₋₆ alkyl, halogen, NR₈R₉, OR₁₂ or COOR₁₂, where R₈, R₉ and R₁₂ are independently hydrogen or C₁₋₆ alkyl; R₅ and R₆ are independently hydrogen or C₁₋₆ alkyl; and R₇ is hydrogen, C₁₋₆ alkyl, C₁₋₆ alkoxy or halogen; and wherein the urea moiety is attached at the 4-, 5- or 6-position of the indole or indoline ring, provided that P is not pyridyl when R₁₀ and R₁₁ form a bond, which has been found to have 5HT_{1C} receptor antagonist activity.

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INDOLE DERIVATIVES AS 5HT_{1C} ANTAGONISTS

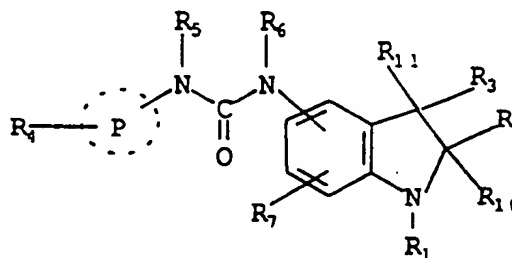
This invention relates to compounds having pharmacological activity, to a process for their preparation, to compositions containing them and to their use in the treatment of mammals.

P. Fludzinski et al., J. Med. Chem. 1986 29 2415-2418 describes N-(1,2-dimethyl-3-ethyl-1H-indol-5-yl)-N'-(3-trifluoromethylphenyl)urea which shows selectivity for the rat stomach fundus serotonin receptor.

10

A class of compounds has now been discovered which have been found to have 5HT_{1C} receptor antagonist activity. 5HT_{1C} receptor antagonists are believed to be of potential use in the treatment of CNS disorders such as anxiety, depression, obsessive compulsive disorders, migraine, anorexia, Alzheimers disease, sleep disorders, bulimia, panic attacks, withdrawal from drug abuse such as cocaine, ethanol, nicotine, and benzodiazepines, schizophrenia, and also disorders associated with spinal trauma and/or head injury, such as hydrocephalus.

Accordingly, the present invention provides a compound of formula (I) or a salt thereof:



25

(I)

wherein:

P represents a quinoline or isoquinoline residue or a 5- or 6-membered aromatic heterocyclic ring containing up to three heteroatoms selected from nitrogen, oxygen or sulphur;

R₁ is hydrogen or C₁₋₆ alkyl;

R₂, R₃, R₁₀ and R₁₁ are independently hydrogen or C₁₋₆ alkyl, or R₁₀ and R₁₁ together form a bond, or R₂ and R₁₀ or R₃ and R₁₁ together form

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a C₂₋₆ alkylene chain;

R₄ is hydrogen, C₁₋₆ alkyl, halogen, NR₈R₉, OR₁₂ or COOR₁₂, where R₈, R₉ and R₁₂ are independently hydrogen or C₁₋₆ alkyl;

R₅ and R₆ are independently hydrogen or C₁₋₆ alkyl; and

- 5 R₇ is hydrogen, C₁₋₆ alkyl, C₁₋₆ alkoxy or halogen; and wherein the urea moiety is attached at the 4-, 5- or 6-position of the indole or indoline ring, provided that P is not pyridyl when R₁₀ and R₁₁ form a bond.

- 10 Alkyl moieties within the variables R₁ to R₁₂ are preferably C₁₋₃ alkyl, such as methyl, ethyl, *n*- and *iso*- propyl, most preferably methyl.

Suitable R₄ and R₇ halogens include chloro and bromo.

- 15 Examples of R₁ include hydrogen, methyl, ethyl and *n*-propyl, preferably methyl.

R₂ and R₃ are preferably hydrogen. R₁₀ and R₁₁ are preferably a bond so as to form an indole structure. In an indoline structure, R₁₀ and R₁₁ are preferably hydrogen.

20

Preferably R₄ is hydrogen or methyl, most preferably hydrogen.

Preferably R₅, R₆ and R₇ are hydrogen.

- 25 The urea moiety can be attached to a carbon or nitrogen atom of the ring P, preferably it is attached to a carbon atom.

- 30 Suitable moieties when the ring P is a 5- or 6-membered aromatic heterocyclic ring include pyrazinyl, pyridazinyl, pyrimidinyl, isothiazolyl, isoxazolyl, thiadiazolyl and triazolyl. When P is a quinoline or isoquinoline residue, the urea moiety can be attached at any position of the ring, preferably to the 4-position.

- 35 The urea moiety is preferably attached at the 5-position of the indole or indoline ring.

The compounds of the formula (I) can form acid addition salts with acids, such as conventional pharmaceutically acceptable acids, for example maleic, hydrochloric, hydrobromic, phosphoric, acetic, fumaric, salicylic, citric, lactic, mandelic, tartaric and methanesulphonic acids.

5

Compounds of formula (I) may also form N-oxides or solvates such as hydrates, and the invention also extends to these forms. When referred to herein, it is understood that the term 'compound of formula (I)' also includes these forms.

10

When R₁ (in an indole) and/or R₅ and/or R₆ are hydrogen or when R₄ is hydroxy or NR₈R₉ and at least one of R₈ and R₉ are hydrogen the compounds of formula (I) may exist tautomerically in more than one form. The invention extends to these and any other tautomeric forms and mixtures thereof.

15

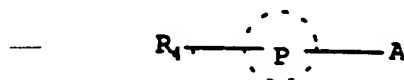
Certain compounds of formula (I) are capable of existing in stereoisomeric forms including enantiomers and the invention extends to each of these stereoisomeric forms and to mixtures thereof including racemates. The different stereoisomeric forms may be separated one from the other by the usual methods, or any given isomer may be obtained by stereospecific or asymmetric synthesis.

20

The present invention also provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof, which process comprises:

25

(a) the coupling of a compound of formula (II);

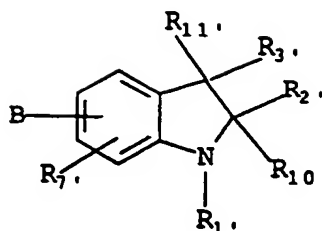


(II)

with a compound of formula (III):

35

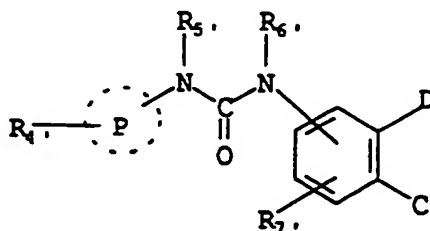
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(III)

- 5 wherein B is attached at the 4-, 5- or 6-position of the indole or indoline ring and A and B contain the appropriate functional group(s) necessary to form the moiety $-NR_5'CONR_6'$ when coupled, wherein R_5' and R_6' are R_5 and R_6 as defined in formula (I) or groups convertible thereto, and the variables R_1' , R_2' , R_3' , R_{10}' , R_{11}' , R_4' and R_7' are R_1 , R_2 , R_3 , R_{10} , R_{11} , R_4 and R_7 respectively, as defined in formula (I), or groups convertible thereto, and thereafter optionally and as necessary and in any appropriate order, converting any R_1' , R_2' , R_3' , R_{10}' , R_{11}' , R_4' , R_5' , R_6' and R_7' when other than R_1 , R_2 , R_3 , R_{10} , R_{11} , R_4 , R_5 , R_6 and R_7 respectively to R_1 , R_2 , R_3 , R_{10} , R_{11} , R_4 , R_5 , R_6 and R_7 , interconverting R_1 , R_2 , R_3 , R_{10} , R_{11} , R_4 , R_5 , R_6 and R_7 , and forming a pharmaceutically acceptable salt thereof; or

(b) cyclising a compound of formula (IV):



(IV)

- 25 wherein R_4' , R_5' , R_6' and R_7' are as defined in formulae (II) and (III) and C and D contain the appropriate functional group(s) necessary to form the indole or indoline ring substituted by R_1' , R_2' , R_3' , R_{10}' , and R_{11}' as defined in formula (III), and thereafter optionally and as necessary in any appropriate order, converting any R_1' , R_2' , R_3' , R_{10}' , R_{11}' , R_4' , R_5' , R_6' and R_7' when other than R_1 , R_2 , R_3 , R_{10} , R_{11} , R_4 , R_5 , R_6 and R_7 , to R_1 , R_2 , R_3 , R_{10} , R_{11} , R_4 , R_5 , R_6 and R_7 , interconverting R_1 , R_2 , R_3 , R_{10} ,

R₁₁, R₄, R₅, R₆ and R₇, and optionally thereafter forming a pharmaceutically acceptable salt.

Suitable examples of groups A and B include:

- 5
- (i) A is -N=C=O and B is -NHR₆' ,
 - (ii) A is -NHR₅' and B is -N=C=O,
 - (iii) A is -NR₅'COL and B is -NHR₆' ,
 - (iv) A is -NHR₅' and B is -NR₆'COL, or
 - 10 (v) A is halogen and B is -NR₆'CONHR₅' ,

wherein R₅' and R₆' are as defined above and L is a leaving group.

Examples of suitable leaving groups L include halogen such as chloro or bromo, imidazole, or phenoxy or phenylthio optionally substituted for example with halogen.

15

When A is -N=C=O and B is NHR₆' or when A is NHR₅' and B is -N=C=O the reaction is suitably carried out in an inert solvent for example dichloromethane or toluene at ambient temperature.

- 20
- When A is -NR₅'COL and B is -NHR₆' or when A is -NHR₅' and B is -NR₆'COL, the reaction is suitably carried out in an inert solvent such as dichloromethane at ambient temperature optionally in the presence of a base, such as triethylamine or in dimethylformamide at ambient or elevated temperature.

25

When A is halogen and B is -NR₆'CONHR₅' , the reaction is suitably carried out in an inert solvent such as toluene at elevated temperature, optionally in the presence of a base.

- 30
- The cyclisation of the compound of formula (IV) to prepare indoles (R₁₀ and R₁₁ are a bond) may be effected using standard methodology such as described in Comprehensive Heterocyclic Chemistry 1984 4, 313 et seq. or J. Het. Chem. 1988 25 p.1 et seq.

- 35
- Examples of the more important routes include the Leimgruber synthesis, the Fischer synthesis and the Japp-Klingemann variation and the Madelung synthesis.

Examples of the groups C and D in the preparation of indoles include:

- (vi) C is NO_2 and D is $\text{CH}=\text{CH}-\text{NZ}_2$ where each Z is independently
 5 C_{1-6} alkyl or together represent C_{2-7} alkylene;
- (vii) C is $\text{NR}_1'-\text{N}=\text{C}(\text{R}_2')-\text{CH}_2\text{R}_3'$ and D is H;
- (viii) C is $\text{NH}-\text{N}=\text{C}(\text{CO}_2\text{X})-\text{CH}_2\text{R}_3'$ and D is H where X is C_{1-6} alkyl;
 10 and
- (ix) C is $\text{NR}_1'\text{COR}_2'$ and D is $\text{CH}_2\text{R}_3'$.

The preparation of indolines includes:

- 15 (x) C is NHR_1' and D is $\text{C}(\text{R}_3')(\text{R}_{11}')\text{C}(\text{R}_2')(\text{R}_{10}')\text{L}$ where L is a leaving group.

Indolines may also be prepared by reduction, e.g. with NaCNBH_3 , of
 20 indoles produced by variants (vi) to (ix) above.

In reaction variant (vi) (Leimgruber synthesis) the compound of formula
 (IV) is prepared from the 2-methylnitrophenyl urea by treatment with a
 dialkylacetal of the dialkylformamide OHCNZ_2 with heating and the
 product of formula (IV) cyclised by hydrogenation over a suitable catalyst
 25 such as palladium and charcoal optionally under pressure to yield the
 compound of formula (I) where $\text{R}_1=\text{R}_2=\text{R}_3=\text{H}$.

In reaction variant (vii) (Fischer synthesis) the compound of formula (IV)
 is prepared from the hydrazinophenyl urea by dehydration, preferably by
 30 heating, with the appropriate ketone $\text{R}_2'\text{COCH}_2\text{R}_3'$ and the product of
 formula (IV) cyclised by heating with an acid catalyst such as hydrochloric
 or sulphuric acid.

In reaction variant (viii) (Japp-Klingemann synthesis) the compound of
 35 formula (IV) is prepared from the aminophenyl urea by diazotisation
 followed by treatment for example with $\text{CH}_3\text{COCH}(\text{CO}_2\text{X})-\text{CH}_2\text{R}_3'$ where
 X is C_{1-6} alkyl under basic conditions in aqueous alcohol as solvent.

The product of formula (IV) may then be cyclised as in the Fischer synthesis above.

- 5 In reaction variant (ix) (Madelung synthesis) the compound of formula (IV) is cyclised with base in an inert solvent optionally with heating.

In reaction variant (x), the compound of formula (IV) is cyclised by heating in an inert solvent, optionally in the presence of a base.

10

It will be appreciated that when D is hydrogen, either or both indole isomers may be formed during the cyclisation process.

- 15 Suitable examples of groups R_2' , R_3' , R_4' , and R_7' which are convertible to R_2 , R_3 , R_4 , and R_7 alkyl groups respectively, include acyl groups which are introduced conventionally and may be converted to the corresponding alkyl group by conventional reduction, such as using sodium borohydride in an inert solvent followed by hydrogenolysis in an inert solvent.
- 20 Hydrogen substituents may be obtained from alkoxycarbonyl groups which may be converted to hydrogen by hydrolysis and decarboxylation. When R_4 is hydroxy it is preferably protected in the compound of formula (II) as, for example, benzyl which is removed by hydrogenation.

- 25 Suitable examples of a group R_1' which is convertible to R_1 , include typical N-protecting groups such as alkoxycarbonyl, in particular *t*-butyloxycarbonyl, acetyl, trifluoroacetyl, benzyl and *para*-methoxybenzyl which are converted to R_1 hydrogen using conventional conditions.

- 30 Suitable examples of groups R_5' and R_6' which are convertible to R_5 and R_6 respectively include alkoxycarbonyl and benzyl or *para*-methoxybenzyl which are converted to R_5 and/or R_6 hydrogen using conventional conditions.

- 35 Interconversions of R_1 , R_2 , R_3 , R_{10} , R_{11} , R_4 , R_5 , R_6 and R_7 are carried out by conventional procedures.

For example, in the case wherein R_1 , R_2 and R_3 are C_{1-6} alkyl and R_5 and R_6 are hydrogen it is possible to introduce a C_{1-6} alkyl group at both the R_5 and R_6 positions by conventional alkylation using 2 molar equivalents of a C_{1-6} alkyl halide and 2 molar equivalents of a suitable base in an inert solvent. Monoalkylation can be achieved using 1 molar equivalent of a C_{1-6} alkyl halide and base using conventional conditions. R_1 C_{1-6} alkyl groups may also be introduced by conventional alkylation, for example using a C_{1-6} alkyl halide and base such as sodium hydride, or by reduction of C_{1-6} acyl.

10

R_4 halo and R_7 halo may be introduced by selective halogenation of the ring P or indole/indoline ring respectively using conventional conditions.

15

It should be appreciated that it may be necessary to protect any R_1 to R_{12} hydrogen variables which are not required to be interconverted.

Protection, especially of a R_1' hydrogen, may also be necessary during coupling reaction (a) and ring-forming reaction (b) above.

20

Suitable protecting groups and methods for their attachment and removal are conventional in the art of organic chemistry, such as those described in Greene T.W. 'Protective groups in organic synthesis' New York, Wiley (1981).

25

It is preferable, however, to introduce and interconvert the groups R_1 to R_{12} before coupling compounds of formulae (II) and (III) together, or cyclising the compound of formula (IV).

30

Compounds of formula (I) which are substituted indoles, and their appropriate derivatives, can be converted to the corresponding indolines, and vice versa, by conventional methods, e.g. reduction with $NaCNBH_3$ in acetic acid and oxidation using MnO_2 in an inert solvent.

35

Compounds of formula (II) in which A is NHR_5' are known compounds or can be prepared analogously to known compounds.

For example, aminopyrazine and 4-aminoquinaldine are commercially available from Aldrich, and 3-amino-6-chloro-pyridazine is commercially available from Lancaster.

5

Compounds of formula (II) in which A is $-N=C=O$ may be prepared by treating a compound of formula (II) in which :

10 i) A is amino, with phosgene or a phosgene equivalent, in the presence of excess base in an inert solvent.

ii) A is acylazide (i.e. CON_3), via the nitrene, by thermal rearrangement using conventional conditions (ref L.S. Trifonov et al., *Helv. Chim. Acta* 1987 70 262).

15

iii) A is $CONH_2$, via the nitrene intermediate using conventional conditions.

20 Compounds of formula (II) in which A is $-NR_5'COL$ may be prepared by reacting a compound of formula (II) in which A is $-NHR_5'$ with phosgene or a phosgene equivalent, in an inert solvent, at low temperature, if necessary in the presence of one equivalent of a base such as triethylamine.

25 Compounds of formula (II) in which A is halogen and R_4' is hydrogen are commercially available.

30 Compounds of formula (III) in which B is NHR_6' are known compounds or can be prepared analogously to known compounds, for example by reduction of the corresponding nitroindole or nitroindoline by catalytic hydrogenation over Pd/C by the method of P. Fludzinski et al. *J. Med. Chem.*, 1986, 29 2415. Specifically, the compound of formula (III) in which R_1' and R_2' are methyl, R_3' is ethyl, R_{10}' and R_{11}' are a bond, R_6' and R_7' are hydrogen and B is NH_2 is prepared using a procedure similar
35 to that described by Fludzinski.

The nitroindoles and nitroindolines are commercially available, for example 5-nitroindole and 5-nitroindoline, or may be prepared conventionally (Comprehensive Heterocyclic Chemistry Vol. 4 p. 313 et seq. (Pergamon Press 1984) and J. Het. Chem. 1988 25 p.1 et seq.)

5

An R_2' alkoxycarbonyl group may be eliminated to give R_2' hydrogen, generally under the conditions effecting formation of the nitroindole or as a subsequent step in the process.

- 10 R_6' alkyl groups may be introduced conventionally, for example by reductive alkylation or acylation and reduction. R_7' C_{1-6} alkyl groups may be introduced ortho to a nitro substituent by alkylation using a procedure similar to that described in G. Bartoli et al., J. Org. Chem. 1986 51 3694 and Tetrahedron 1987 43 4221.

15

Compounds of formula (III) in which B is $-N=C=O$ may be prepared by treating a compound of formula (III) in which :

- 20 i) B is amino, with phosgene or a phosgene equivalent, in the presence of excess base in an inert solvent.
- ii) B is acylazide (i.e. CON_3), via the nitrene, by thermal rearrangement using conventional conditions.
- 25 iii) B is $CONH_2$, via the nitrene intermediate using conventional conditions.

- Compounds of formula (III) in which B is $-NR_6'COL$ may be prepared by reacting a compound of formula (III) in which B is $-NHR_6'$ with phosgene or a phosgene equivalent, in an inert solvent, at low temperature, if necessary in the presence of one equivalent of a base such as triethylamine.
- 30

- Compounds of formula (III) in which B is $-NR_6'CONHR_5'$ can be prepared from the corresponding precursor where B is NHR_6' by reaction with an R_5' isocyanate under conventional conditions.
- 35

Examples of phosgene equivalents include triphosgene, carbonyldiimidazole, phenyl chloroformate and phenyl chlorothioformate.

Novel intermediates of formula (III) also form part of the invention.

5

Compounds of formula (IV) may be prepared from the appropriate aminophenyl derivative analogously to compounds of formula (I).

Novel intermediates of formula (IV) also form part of the invention.

10

Pharmaceutically acceptable salts may be prepared conventionally by reaction with the appropriate acid or acid derivative.

N-oxides may be formed conventionally by reaction with hydrogen peroxide or percarboxylic acids.

15

Compounds of formula (I) and their pharmaceutically acceptable salts have 5HT_{1C} receptor antagonist activity and are believed to be of potential use in the treatment or prophylaxis of anxiety, depression, migraine, anorexia, obsessive compulsive disorders, Alzheimer's disease, sleep disorders, bulimia, panic attacks, withdrawal from drug abuse such as cocaine, ethanol, nicotine, and benzodiazepines, schizophrenia, and also disorders associated with spinal trauma and/or head injuries, such as hydrocephalus.

25

Thus the invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use as a therapeutic substance, in particular in the treatment or prophylaxis of anxiety, depression, migraine, anorexia, obsessive compulsive disorders, Alzheimer's disease, sleep disorders, bulimia, panic attacks, withdrawal from drug abuse such as cocaine, ethanol, nicotine, and benzodiazepines, schizophrenia, and also disorders associated with spinal trauma and/or head injuries, such as hydrocephalus.

30

The invention further provides a method of treatment or prophylaxis of anxiety, depression, migraine, anorexia, obsessive compulsive disorders, Alzheimer's disease, sleep disorders, bulimia, panic attacks, withdrawal

35

from drug abuse such as cocaine, ethanol, nicotine, and benzodiazepines, schizophrenia, and also disorders associated with spinal trauma and/or head injuries, in mammals including humans, which comprises administering to the sufferer a therapeutically effective amount of a
5 compound of formula (I) or a pharmaceutically acceptable salt thereof.

In another aspect, the invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment or prophylaxis of anxiety,
10 depression, migraine, anorexia, obsessive compulsive disorders, Alzheimer's disease, sleep disorders, bulimia, panic attacks, withdrawal from drug abuse such as cocaine, ethanol, nicotine, and benzodiazepines, schizophrenia, and also disorders associated with spinal trauma and/or head injuries.

15 The present invention also provides a pharmaceutical composition, which comprises a compound of formula (I) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

20 A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for oral, parenteral or rectal administration and, as such, may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable or infusable
25 solutions or suspensions or suppositories. Orally administrable compositions are generally preferred.

Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents, fillers,
30 tabletting lubricants, disintegrants and acceptable wetting agents. The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or
35 oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional

additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and, if desired, conventional flavourings or colourants.

- 5 For parenteral administration, fluid unit dosage forms are prepared utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved for
10 injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are
15 prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilization cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the
20 composition to facilitate uniform distribution of the compound.

The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration.

25

- The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 to 1000 mg, more suitably
30 0.05 to 20.0 mg, for example 0.2 to 5 mg; and such unit doses may be administered more than once a day, for example two or three a day, so that the total daily dosage is in the range of about 0.01 to 100 mg/kg; and such therapy may extend for a number of weeks or months.

- 35 When administered in accordance with the invention, no unacceptable toxicological effects are expected with the compounds of the invention.

The following Examples illustrate the preparation of pharmacologically active compounds of the invention. The following Descriptions illustrate the preparation of intermediates to compounds of the present invention.

5 Description 1

1-Methyl-5-nitro-1H-indole (D1)

To a stirred suspension of sodium hydride (5.0g; 167 mmol) in
10 dimethylformamide (200 ml) at 0°C under nitrogen was added 5-nitroindole (25g; 154 mmol) in dimethylformamide. After stirring for 0.5h, iodomethane (10.5 ml; 168 mmol) in dimethylformamide (50 ml) was added, and stirring was continued for 2h. The reaction mixture was then quenched with water, and poured onto excess water with stirring.
15 Filtration afforded the title compound (27.4g; 94%).

NMR (CDCl₃) δ : 3.88 (3H, s), 6.68 (1H, d, J=3), 7.21 (1H, d, J=3), 7.34 (1H, d, J=8, 2), 8.13 (1H, dd, J=8, 2), 8.59 (1H, d, J=2).

20 Description 2

5-Amino-1-methyl-1H-indole (D2)

A mixture of the nitroindole (D1) (5g; 28.4 mmol) and 5% palladium on
25 charcoal in ethanol (300 ml) was hydrogenated at 60 p.s.i. (4.14×10^5 Pa) at room temperature for 3h. Removal of the catalyst by filtration followed by evaporation of the solvent gave the title compound (3.39g, 95%).

30 NMR (CDCl₃) δ : 3.20 (2H, broad s), 3.70 (3H, s), 6.28 (1H, d, J=3), 6.68 (1H, dd, J=8, 2), 6.92 (1H, d, J=2), 6.96 (1H, d, J=3), 7.12 (1H, d, J=8).

Description 3

35 Phenyl N-(1-Methyl-1H-indol-5-yl) carbamate (D3)

To a solution of phenyl chloroformate (2.21 ml; 17.4 mmol) in dry

tetrahydrofuran (30 ml), cooled in a carbon tetrachloride / solid carbon dioxide bath, was added 5-amino-1-methylindole (D2) (2.31g; 15.8 mmol) followed by triethylamine (2.40 ml; 17.4 mmol). The mixture was stirred for 45 min at -20°C (bath temperature), then evaporated. The residue was
5 dissolved in ethyl acetate, washed with brine, dried and evaporated to give the title compound (4.29g; 100%), m.p. 103-107°C (EtOAc/petrol).

NMR (CDCl₃) δ : 3.80 (3H, s), 6.45 (1H, d, J=3), 6.93 (1H, broad s), 7.05
10 (1H, d, J=3), 7.25 (5H, m), 7.40 (2H, dd, J=8, 8), 7.74 (1H, broad s).

Description 4

Pyrimidine-5-carboxylic acid (D4)

15 n-Butyllithium (1.6M in hexane, 6.9 ml, 11 mmol) was added to dry THF (10 ml) and the solution was cooled to -100°C. A solution of 5-bromopyrimidine (1.59g, 10 mmol) in dry THF (50 ml) was added slowly. After 15 min at -80 to -100°C, the mixture was added dropwise onto solid
20 carbon dioxide in dry THF. After warming to room temperature, the mixture was made slightly acidic with dilute sulphuric acid. The solid was filtered off and extracted with ethanol. The extract was filtered and evaporated and the residue was re-extracted with methanol. Evaporation of solvent gave the title compound (1.48g, 100%).

25 NMR (d₄ - MeOH) δ : 9.17 (1H, s), 9.20 (2H, s).

m/z (EI): 124 (M⁺)

30 Example 1

N-(1-Methyl-5-indolyl)-N'-(2-pyrazinyl) urea (E1)

To a suspension of sodium hydride (80% in oil, 0.66g, 22 mmol) in dry
35 DMF (50 ml) was added 2-aminopyrazine (0.95g, 10 mmol). After hydrogen evolution had ceased (15 min), phenyl N-(1-methyl-5-indolyl) carbamate (D3) (2.67g, 10 mmol) was added, followed by a further portion

of sodium hydride (0.2g). The mixture was stirred overnight at room temperature and then evaporated *in vacuo*. The residue was dissolved in dichloromethane/methanol and washed with water and brine. The organic phase was dried and evaporated and the residue was triturated with dichloromethane/petrol. The residue was then recrystallised from DMSO/water to give the title compound (1.09g). m.p. 222-226°C.

Found: C, 62.75; H, 4.83; N, 26.10

C₁₄H₁₃N₅O requires: C, 62.91; H, 4.90; N, 26.20%

NMR (D₆-DMSO) δ : 3.78 (3H, s), 6.38 (1H, d, J=3), 7.19 (1H, dd, J=8, 2), 7.30 (1H, d, J=3), 7.38 (1H, d, J=8), 7.77 (1H, d, J=2), 8.22 (1H, d, J=2), 8.30 (1H, m), 9.01 (1H, s), 9.52 (1H, s), 9.57 (1H, s).

Example 2

N-(1-Methyl-5-indolyl)-N'-(3-pyridazinyl) urea (E2)

The title compound (0.53g) was prepared by the method of Example 1, using sodium hydride (0.59g, 19.7 mmol), 3-aminopyridazine (0.85g, 8.95 mmol) and carbamate (D3) (2.39g, 8.95 mmol) in DMF (40 ml). mp. 220-225°C, 96.5% pure by HPLC.

NMR (d₆-DMSO) δ : 3.78 (3H, s), 6.38 (1H, d, J=3), 7.18 (1H, dd, J=8, 2), 7.30 (1H, d, J=3), 7.39 (1H, d, J=8), 7.72 (1H, dd, J=5, 9), 7.75 (1H, d, J=2), 8.0 (1H, d, J=9), 8.85 (1H, d, J=5), 9.69 (1H, s), 9.73 (1H, s).

m/z (EI): 267 (M⁺), 172, 146.

Example 3

N-(1-Methyl-5-indolyl)-N'-(5-pyrimidinyl) urea (E3)

A mixture of acid (D4, 1.22g, 9.8 mmol), 5-amino-1-methyl indole (D2, 1.43g, 9.8 mmol), triethylamine (1.4 ml) and diphenylphosphoryl azide

(2.1 ml, 10 mmol) in 1,4-dioxan (100 ml) was heated under reflux overnight. The mixture was evaporated and the residue was dissolved in dichloromethane and washed with 5% citric acid, sat. sodium bicarbonate and water. The organic phase was dried and evaporated and the residue
5 was chromatographed on silica (100g) eluted with 2-15% methanol/dichloromethane. Combination of appropriate fractions followed by recrystallisation from dichloromethane/methanol gave pure (E3, 0.70g). mp 210-213°C.

10 Found: C, 62.93; H, 4.84; N, 26.06.

$C_{14}H_{13}N_5O$ requires C, 62.91; H, 4.90; N, 26.20%

NMR (d_6 -DMSO) δ : 3.76 (3H, s), 6.37 (1H, d, J=3), 7.17 (1H, dd, J=8,
15 2), 7.29 (1H, d, J=3), 7.37 (1H, d, J=8), 7.69 (1H, d, J=2), 8.78 (2H, s), 8.91 (3H, s).

Example 4

N-(1-Methyl-5-indolyl)-N'-(4-pyridazinyl) urea (E4)

20

The title compound was prepared by the method of Example 3, using pyridazine-4-carboxylic acid (0.5g, 4 mmol), aminoindole (D2, 0.59g, 4 mmol), triethylamine (0.57 ml) and diphenylphosphoryl azide (0.86 ml, 4.1 mmol) in 1,4-dioxan (40 ml). Crude product was chromatographed on
25 silica (75g) eluted with 5-10% methanol/dichloromethane. The second component was extracted with hot methanol to give an insoluble residue of pure title compound (0.11g). mp 216-221°C.

Found: C, 62.17; H, 4.85; N, 25.49

30 $C_{14}H_{13}N_5O$ requires: C, 62.91; H, 4.90; N, 26.20%

NMR (d_6 -DMSO) δ : 3.78 (3H, s), 6.38 (1H, d, J=3), 7.18 (1H, dd, J=8,
35 2), 7.30 (1H, d, J=3), 7.38 (1H, d, J=8), 7.70 (1H, d, J=2), 7.81 (1H, dd, J=6, 3), 8.88 (1H, s), 8.91 (1H, d, J=6), 9.20 (1H, d, J=3), 9.29 (1H, s).

Example 5**N-(1-Methyl-5-indolyl)-N'-(3-methyl-5-isothiazolyl) urea (E5)**

5

To a suspension of sodium hydride (80% in oil, 0.99mg, 3.3 mmol in dry DMF (5 ml) was added 5-amino-3-methylisothiazole hydrochloride (0.15mg, 1mmol). After hydrogen evolution had ceased (15 min), phenyl N-(1-methyl-5-indolyl) carbamate (D3) (0.267mg, 1 mmol) was added.

10

The mixture was stirred overnight at room temperature and then evaporated *in vacuo*. The residue was dissolved in dichloromethane/methanol and the solution was washed with water and brine, dried and evaporated. The crude product was triturated with
15 dichloromethane/petrol and the residue was chromatographed on silica (10 g) eluted with 2% methanol/dichloromethane. Recrystallisation from dichloromethane/petrol gave the title compound (0.10g). mp. 186-189°C, 99.6% pure by HPLC.

20 NMR (CDCl₃): δ : 2.32 (3H, s), 3.78 (3H, s), 6.32 (1H, s), 6.44 (1H, d, J=3), 7.08 (1H, d, J=3), 7.18 (1H, dd, J=8, 2), 7.27 (1H, d, J=8), 7.64 (1H, d, J=2).

m/z (EI): 286 (M⁺), 172, 146.

25

Example 6**N-(1-Methyl-5-indolyl)-N'-(3-methyl-5-isoxazolyl) urea (E6)**

30 The title compound was prepared by the method of Example 5, using 5-amino-3-methylisoxazole (0.098g, 1 mmol), sodium hydride (0.066g, 2.2 mmol) and carbamate (D3, 0.267g, 1 mmol) in dry DMF (5 ml). The crude product was triturated with dichloromethane/petrol, then recrystallised from dichloromethane/methanol/petrol to give the title compound (0.135g).
35 mp 186-189°C, 97.5% pure by HPLC.

NMR (d_6 -DMSO) δ : 2.07 (3H, s), 3.67 (3H, s), 5.84 (1H, s), 6.27 (1H, d, $J=3$), 7.04 (1H, dd, $J=8, 2$), 7.18 (1H, d, $J=3$), 7.26 (1H, d, $J=8$), 7.58 (1H, d, $J=2$), 8.53 (1H, s).

5 m/z (EI): 270 (M^+), 172

Example 7

N-(1-Methyl-5-indolyl)-N'-(2-(1,3,4-thiadiazolyl)) urea (E7)

10

A mixture of 2-amino-1,3,4-thiadiazole (1.01g, 10 mmol), carbamate (D3, 2.67g, 10 mmol), and N-methylmorpholine (1.2 ml) in DMF (100 ml) was heated at 100-140°C overnight, then cooled and evaporated. The residue was dissolved in dichloromethane/methanol and washed with brine and
15 water. The organic phase was dried and evaporated, and the residue was recrystallised from dichloromethane/methanol/petrol to give the title compound (1.54g). mp 217-220°C (decomp.).

Found: C, 52.35; H, 4.07; N, 25.29

20 $C_{12}H_{11}N_5OS$ requires C, 52.73; H, 4.06; N, 25.62%

NMR (d_6 -DMSO) δ : 3.78 (3H, s), 6.38 (1H, d, $J=3$), 7.18 (1H, d, $J=8$), 7.32 (1H, d, $J=3$), 7.39 (1H, d, $J=8$), 7.73 (1H, s).

25 Example 8

N-(1-Methyl-5-indolyl)-N'-(4-(1,2,4-triazolyl)) urea (E8)

To a solution of 1,1'-carbonyldiimidazole (0.27g) in dichloromethane (10
30 ml) at 0°C was added aminomethylindole (D2, 0.22g, 1.5 mmol) in dichloromethane (10 ml). The mixture was stirred at 0°C for 15 min, then evaporated and the residue was redissolved in dry DMF (10 ml). 4-Amino-1,2,4-triazole (0.134g, 1.6 mmol) was added in DMF (2.5 ml) and the mixture was heated at 120-140°C for 1h, then poured into water. The
35 aqueous solution was filtered and evaporated to dryness, and the residue was chromatographed on silica (25g) eluted with 5-10% methanol/dichloromethane. The second-eluted material was the title

compound (0.21g). mp 202-206°C.

Found: C, 56.36; H, 4.82; N, 32.65

C₁₂H₁₂N₆O requires: C, 56.24; H, 4.72; N, 32.79%

5

NMR (d₆-DMSO) δ: 3.77 (3H, s), 6.35 (1H, d, J=3), 7.18 (1H, dd, J=8, 2), 7.29 (1H, d, J=3), 7.35 (1H, d, J=8), 7.65 (1H, d, J=2).

10 Example 9

N-(1-Methyl-5-indolyl)-N'-(3-quinolyl)-urea hydrochloride (E9)

15 A stirred suspension of carbonyl diimidazole (0.34g, 2.1 mmol) in dry dichloromethane (5 ml) was treated with a solution of 5-amino-1-methylindole (D2, 0.29g, 2 mmol) in dry dichloromethane (5 ml).

20 After 0.25h, the reaction mixture was evaporated to dryness and the residue dissolved in DMF (10 ml). 3-Aminoquinoline (0.32g 2.2 mmol) was added and the reaction mixture heated to 90°C for 1h then cooled and added to water (200 ml) with vigorous stirring. The precipitate was filtered, dried and recrystallised from ethanol affording the product as an off-white solid (0.4g, 66% yield). This was converted into the title compound using HCl in ether. mp 230°C (from ethanol)

25

Found: C, 64.42; H, 4.72; N, 15.71.

C₁₉H₁₇N₄OCl requires: C, 64.68; H, 4.82; N, 15.87%

30 NMR (d₆-DMSO) δ: 3.77 (3H, s), 6.38 (1H, d, J=6), 7.2-7.4 (3H, m), 7.77 (3H, m), 8.1 (2H, m), 8.80 (1H, d, J=3), 9.19 (2H, d, J=12), 9.79 (1H, s).

Example 10

35 N-(1-Methyl-5-indolyl)-N'-(6-quinolyl)-urea hydrochloride (E10)

A stirred suspension of carbonyl diimidazole (0.34g, 2.1 mM) in dry

dichloromethane (5 ml) was treated with a solution of 5-amino 1-methyl indole (D2, 0.29g, 2 mM) in dry dichloromethane (5 ml). After 0.25h, the reaction mixture was evaporated to dryness and the residue dissolved in DMF (10 ml). 6-Aminoquinoline (0.32g, 2.2 mM) was added and the reaction mixture heated to 90°C for 1h then cooled and added to water (200 ml) with vigorous stirring. The precipitate was filtered, dried and recrystallised from ethanol, affording the product as a white solid (0.32g, 51%). This was converted into the hydrochloride salt (E2) using HCl in ether. mp 208°C (from ethyl acetate).

10

NMR (d⁶-DMSO) δ : 3.77 (3H, s), 6.38 (1H, d, J=3), 7.2-7.4 (3H, m), 7.7-8.2 (4H, m), 8.48 (1H, s), 8.8-9.1 (3H, m), 9.58 (1H, s).

15 m/z (EI): 316 (M⁺, C₁₉H₁₆N₄O)

Example 11

N-(1-Methyl-5-indolyl)-N'-(8-quinolyl) urea (E11)

20

The title compound was prepared from 8-aminoquinoline, 1, 1'-carbonyl diimidazole and 5-amino-1-methyl-indole (D2) using a procedure similar to that described for Example 10, in 31% yield, m.p. 205-209° C.

25 NMR (D₆-DMSO) δ : 3.76 (3H, s), 6.35 (1H, d, J 3), 7.22 (1H, dd, J 6, 2), 7.27 (1H, d, J 3), 7.36 (1H, d, J 6), 7.5-7.54 (2H, m), 7.60-7.65 (1H, m), 7.8 (1H, s), 8.39 (1H, d, J 6), 8.57 (1H, m), 8.92 (1H, d, J 2), 9.62 (2H, s).

30 Found: M⁺316
C₁₉H₁₆N₄O requires 316

Example 12

35 N-(1-Methyl-5-indolyl)-N'-(5-quinolyl) urea (E12)

The title compound was prepared from 5-aminoquinoline, 1, 1'-carbonyl

-22-

diimidazole and 5-amino-1-methyl-indole (D2) using a procedure similar to that described for Example 10, in 20% yield, m.p 243-245° C.

5 NMR (D₆-DMSO)δ: 3.76 (3H, s), 6.35 (1H, d, J 2), 7.20 (1H, d, J 6), 7.29 (1H, d, J 2), 7.38 (1H, d, J 6), 7.60-7.65 (1H, m), 7.72 (2H, d, J 3), 7.77 (1H, s), 8.10 (1H, t, J 2), 8.57 (1H, d, J 6) 8.84 (2H, d, J 3), 8.93 (1H, d, J 2)

Found: M⁺ 316

10 C₁₉H₁₆N₄O requires 316

Example 13

15 N-(1-Methyl-5-indolyl)-N'-(2-methyl-4-quinolyl) urea hydrochloride (E13)

20 The title compound was prepared from 4-aminoquinaldine, 1,1'-carbonyl diimidazole and 5-amino-1-methyl-indole (D2) using a procedure similar to that described for Example 10 and then converted to the hydrochloride salt, in 24% overall yield, m.p. 215-220° C.

25 NMR (D₆-DMSO)δ: 2.80 (3H, s), 3.77 (3H, s), 6.39 (1H, d, J 2), 7.23-7.33 (2H, m), 7.42 (1H, d, J 6), 7.79-7.84 (2H, m), 8.0-8.11 (2H, dd J 6,6), 8.60 (1H, s), 9.08 (1H, d, J 8), 10.8 (1H, s), 10.92 (1H, s), 15.0 (1H, broad s).

Found: M⁺ 330

C₂₀H₁₈N₄O requires 330

30 Example 14

N-(1-methyl-5-indolyl)-N'-(6-Isoquinolyl) urea (E14)

35 The title compound is prepared using standard methodology as described herein, such as reaction of (D2) with carbonyl diimidazole in a solvent such as dry dichloromethane, and reacting the product with 6-aminoisoquinoline in a solvent such as DMF, with heating.

Example 15**N-(1-Methyl-5-indolyl)-N'-(5-isoquinolyl) urea (E15)**

5 To a solution of carbonyl diimidazole (0.31g, 2.15 mmol) in dichloromethane (20 ml) was added 5-aminoisoquinoline (0.25g, 1.7 mmol) in dichloromethane (20 ml). After stirring at room temperature for 0.5 h, the solution was evaporated to dryness. The residue was taken up in
10 dimethylformamide (20 ml) and to this solution was added 5-amino-1-methyl-indole (D2) (0.25g, 1.7 mmol) in dimethylformamide (20 ml). The reaction mixture was heated to 90° C for 1h, then cooled and added dropwise to water, with vigorous stirring. The resulting suspension was filtered off, washed with water and dried in *vacuo* to yield the title
15 compound in 53% yield, m.p. 254-259° C.

NMR (D₆-DMSO)δ: 3.77 (3H, s), 6.37 (1H, d, J 3), 7.19 (1H, dd J 6,2),
7.28 (1H, d, J 3), 7.37 (1H, d, J 8), 7.65 (1H, t, J 6),
7.75-7.8 (2H, m), 7.99 (1H, d, J 6), 8.32 (1H, d, J 6),
20 8.57 (1H, d, J 6), 8.84 (2H, d, J 8), 9.29 (1H, s).

Found: M⁺ 316

C₁₉H₁₆N₄O requires 316

25 Example 16**N-(1-Methyl-5-indolyl)-N'-(1-isoquinolyl) urea (E16)**

The title compound was prepared from 1-aminoisoquinoline, 1, 1'-carbonyl
30 diimidazole and 5-amino-1-methyl-indole (D2) using a procedure similar to that described for Example 15, in 11% yield, m.p. 230-233° C.

NMR (CDCl₃)δ: 3.81 (3H, s), 6.47 (1H, d, J 2), 7.07 (1H, d, J 3), 7.30
(2H, m), 7.46 (1H, dd J 6,2), 7.61-7.82 (3H, m), 7.97
35 (1H, s), 8.09-8.16 (3H, m), 12.4 (1H, broad s).

Found: M^+ 316

$C_{19}H_{16}N_4O$ requires 316

Example 17

5

N-(1-Methyl-5-indolyl)-N'-(4-isoquinolyl) urea (E17)

10 The title compound was prepared from 4-aminoisoquinoline, 1,1'-carbonyl diimidazole and 5-amino-1-methyl-indole using a procedure similar to that described for Example 1, and then converted to the hydrochloride salt using hydrogen chloride in ether/ethanol, in 26% overall yield, m.p. 195-197° C.

15 NMR (D_6 -DMSO) δ : 3.77 (3H, s), 6.39 (1H, d, J 2), 7.22 (1H, dd J 6,2), 7.32 (1H, d, J 3), 7.4 (1H, d, J 6), 7.80 (1H, s), 7.94 (1H, t, J 6), 8.13 (1H, t, J 6), 8.39 (1H, d, J 6), 8.55 (1H, d, J 6), 9.24 (1H, s), 9.34 (1H, s), 9.50 (2H, d, J 8).

20 Found: M^+ 316

$C_{19}H_{16}N_4O$ requires 316

Pharmacological data

[³H]-mesulergine binding to pig choroid plexus membranes in vitro

Evidence from the literature suggests that 5-HT_{1C} antagonists may have a number of therapeutic indications including the treatment of anxiety, migraine, depression, feeding disorders and obsessive compulsion disorders. (Curzon and Kennett, 1990; Fozard and Gray, 1989) and Alzheimer's Disease (Lawlor, 1989, J. Arch. Gen. Psychiat. Vol. 46 p.542).

The affinity of test drugs for the 5-HT_{1C} binding site can be determined by assessing their ability to displace [³H]-mesulergine from 5-HT_{1C} binding sites in pig choroid plexus membranes. The method employed was similar to that of Pazos et al., 1984.

Pooled pig choroid plexi were homogenised in 20 vols of Tris HCl buffer (pH7.4) (containing 4mM CaCl₂ and 0.01% ascorbic acid) and centrifuged at 50,000g for 15 min at 4°C. The supernatant was removed and re-centrifuged. This was repeated a further two times with the incubation of the homogenate (37°C for 15 min) before the final centrifugation. The final pellet was resuspended in 20vols of buffer and stored at -70°C until use.

The tissue suspension (50ml) was incubated with [³H]-mesulergine (2nM) in Tris HCl buffer (pH7.4) at 37°C (containing 0.01% ascorbic acid, 4mM CaCl₂) and 3 x 10⁻⁸M spiperone for 30 minutes. Non-specific binding was measured in the presence of mianserin (10⁻⁶M). Six concentrations of test drug (10⁻⁹ to 10⁻⁴M final concentration) were added in a volume of 50ml. The total assay volume was 500ml. Incubation was stopped by rapid filtration using a Skatron cell harvester and radioactivity measured by liquid scintillation spectrometry. The IC₅₀ values were determined and the pK_i (the negative logarithm of the inhibition constant) calculated from the Cheng Prusoff equation where

$$\frac{K_i = IC_{50}}{1 + \frac{C}{K_d}}$$

5

K_i = inhibition constant.

C = concentration of [3 H]-mesulergine

K_d = Affinity of mesulergine for 5-HT $_1$ C binding sites.

- 10 Curzon, G.A. and Kennett, G.A. (1990). TIPS, Vol. 11, 181-182.
Fozard, J.R. and Gray, J.A. (1989). TIPS, Vol. 10, 307-309.
Pazos, A. et al. (1984). Eur. J. Pharmacol., 106, 531-538.

15 **[3 H]-Mesulergine binding to rat 5-HT $_1$ C clones expressed in 293 cells in vitro**

The affinity of test drugs for the 5-HT $_1$ C binding site can be determined by assessing their ability to displace [3 H]-mesulergine from 5-HT $_1$ C clones expressed in 293 cells (Julius et al., 1988). The method employed
20 was similar to that of Pazos et al., 1984.

The cells suspension (50 μ l) was incubated with [3 H]-mesulergine (0.5 nM) in Tris HCl buffer (pH 7.4) at 37°C for 30 minutes. Non-specific binding was measured in the presence of mianserin (10 $^{-6}$ M). Ten
25 concentrations of test drug (3 x 10 $^{-9}$ to 10 $^{-4}$ M final concentration) were added in a volume of 50 μ l. The total assay volume was 500 μ l. Incubation was stopped by rapid filtration using a Brandel cell harvester and radioactivity measured by scintillation counting. The IC $_50$ values were determined using a four parameter logistic program (DeLean 1978)
30 and the pK $_i$ (the negative logarithm of the inhibition constant) calculated from the Cheng + Prusoff equation.

Julius et al. (1988) Science 241, 558-564.

- 35 DeLean A, Munson P.J., Rodbaud D. (1978) Am. J. Physiol. 235, E97-E102.

The compounds of examples 3 -7, 12, 13, 15 and 17 have pK_i values in the range 5.97 to 8.3.

Reversal of MCPP-induced Hypolocomotion

- 5 Administration of m-(chlorophenyl)piperazine (mCPP) to rats induces hypolocomotion (Kennett and Curzon 1988, Luckie *et al.* 1989) as seen with the related drug 1-(m-trifluoromethylphenyl)piperazine (TFMPP) (Lucki and Frazer 1982, Kennett and Curzon 1988). This effect was
- 10 blocked by the non specific 5-HT_{1C}/5-HT₂ receptor antagonists mianserin, cyproheptadine and metergoline and perhaps by mesulergine. It was not blocked by the 5-HT₂ receptor antagonists ketanserin and ritanserin at relevant doses (Kennett and Curzon 1991) nor by
- 15 antagonists of 5-HT_{1A}, 5-HT_{1B}, 5-HT₃, α_2 adrenoceptors or dopamine D₂ receptors. The effect of mCPP is therefore considered to be mediated by 5-HT_{1C} receptors (Kennett and Curzon 1988) as confirmed by subsequent studies (Lucki *et al.*, 1989). Since mCPP causes hypolocomotion when infused into the cerebral ventricles this effect is probably centrally mediated (Kennett and Curzon 1988).
- 20 mCPP-induced hypolocomotion was measured in automated locomotion cages of dimensions 56 cm long x 16½ cm wide x 25 cm high and made of black perspex. Two photobeams traversed the width of the cages at either end at ground level. Sequential breaking of these beams allowed the
- 25 measurement of cage transits.
- Male Sprague Dawley rats (200-250g) (Charles River) were housed in groups of six. They were given drugs orally 1h pretest and 40 mins later mCPP (7 mg/kg i.p.). After a further 20 min they were placed in
- 30 individual automated cages in groups of four under red light in an adjacent room. After 10 min the test was terminated. Reversal of mCPP-induced hypolocomotion was considered as evidence of *in vivo* central 5-HT_{1C} receptor antagonist properties.
- 35 Kennett, G.A., Curzon, G., (1988). *Brit. J. Pharmacol.* 94, 137-147.
Kennet G.A., Curzon, G., (1991). *Brit.J. Pharmacol.* 103, 2016-2020.
Lucki, I., Frazer, A., (1982) *Am. Soc. Neurosci.* 8(abstr.), 101.

Lucki, I., Ward, M.R., Frazer, A., (1989). J.Pharmacol. Exp. Therap. 249, 155-164.

5 The compound of Examples 2 and 3 had ID₅₀ values of 47.0 and 43.7 mg/kg p.o.

Rat Fundus: 5-HT_{1C}-like Receptors

10 Introduction

The 5-HT receptor in the rat fundic strip (RFS) has been characterised as '5-HT_{1C}-like' as its pharmacology is similar, but not identical, to that of rat 5-HT_{1C} receptor clones. Hence this tissue may be used to assess the 5-HT_{1C}-like antagonist properties of compounds.

15 Methods

20 Whole stomachs were obtained from male CD Rats (Charles River, 250-350g). Strips of fundus (2cm x 0.5 cm) were cut from the greater curvature and the mucosae carefully removed. Tissues were then further dissected into smaller strips (2 mm x 20 mm) which were mounted in organ baths containing oxygenated Tyrodes solution at 37°C containing indomethacin (3 µM). Preparations were maintained under a resting tension of 0.5g and exposed to the irreversible MAO inhibitor pargyline
25 (100 µM for 30 minutes followed by washout). Over a 1h equilibration period, rat fundic strips were challenged with 1×10^{-8} M 5-HT at 15 minute intervals until constant responses were obtained. Fifteen minutes later, a complete cumulative concentration-effect curve to the standard agonist 5-HT (1×10^{-10} upwards) was constructed to determine the
30 individual sensitivity of each preparation. A further concentration-effect curve to either 5-HT, or other agonists was constructed no sooner than 1h after completion of the previous curve. When necessary tissues were equilibrated with the antagonists over this one hour period. Antagonists affinities are expressed as pA₂ estimates.

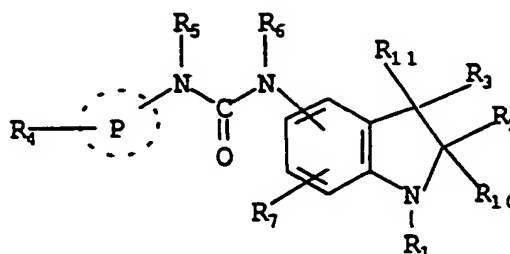
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Results

The compound of Example 5 had a pA_2 value of 7.9.

Claims:

1. A compound of formula (I) or a salt thereof:



(I)

- 10 wherein:

P represents a quinoline or isoquinoline residue or a 5- or 6-membered aromatic heterocyclic ring containing up to three heteroatoms selected from nitrogen, oxygen or sulphur;

R₁ is hydrogen or C₁₋₆ alkyl;

- 15 R₂, R₃, R₁₀ and R₁₁ are independently hydrogen or C₁₋₆ alkyl, or R₁₀ and R₁₁ together form a bond, or R₂ and R₁₀ or R₃ and R₁₁ together form a C₂₋₆ alkylene chain;

R₄ is hydrogen, C₁₋₆ alkyl, halogen, NR₈R₉, OR₁₂ or COOR₁₂, where R₈, R₉ and R₁₂ are independently hydrogen or C₁₋₆ alkyl;

- 20 R₅ and R₆ are independently hydrogen or C₁₋₆ alkyl; and

R₇ is hydrogen, C₁₋₆ alkyl, C₁₋₆ alkoxy or halogen; and wherein the urea moiety is attached at the 4-, 5- or 6-position of the indole or indoline ring, provided that P is not pyridyl when R₁₀ and R₁₁ form a bond.

- 25 2. A compound according to claim 1 in which R₁ is methyl.

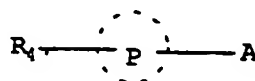
3. A compound according to claim 2 in which R₂ and R₃ are hydrogen.

- 30 4. A compound according to claim 3 in which R₁₀ and R₁₁ are both hydrogen or R₁₀ and R₁₁ together form a bond to form an indole structure.

5. A compound according to claim 4 in which R₄, R₅, R₆ and R₇ are hydrogen.
6. A compound according to any one of claims 1 to 5 in which the
5 urea moiety is attached at the 5-position of the indole or indoline ring.
7. A compound according to claim 1 which is selected from
N-(1-methyl-5-indolyl)-N'-(2-pyrazinyl) urea,
N-(1-methyl-5-indolyl)-N'-(3-pyridazinyl) urea,
10 N-(1-methyl-5-indolyl)-N'-(5-pyrimidinyl) urea,
N-(1-methyl-5-indolyl)-N'-(4-pyridazinyl) urea,
N-(1-methyl-5-indolyl)-N'-(3-methyl-5-isothiazolyl) urea,
N-(1-methyl-5-indolyl)-N'-(3-methyl-5-isoxazolyl) urea,
N-(1-methyl-5-indolyl)-N'-(2-(1,3,4-thiadiazolyl)) urea,
15 N-(1-methyl-5-indolyl)-N'-(4-(1,2,4-triazolyl)) urea,
N-(1-methyl-5-indolyl)-N'-(3-quinolyl)-urea,
N-(1-methyl-5-indolyl)-N'-(6-quinolyl)-urea,
N-(1-methyl-5-indolyl)-N'-(8-quinolyl) urea,
N-(1-methyl-5-indolyl)-N'-(5-quinolyl) urea,
20 N-(1-methyl-5-indolyl)-N'-(2-methyl-4-quinolyl) urea,
N-(1-methyl-5-indolyl)-N'-(6-Isoquinolyl) urea,
N-(1-methyl-5-indolyl)-N'-(5-isoquinolyl) urea,
N-(1-methyl-5-indolyl)-N'-(1-isoquinolyl) urea,
N-(1-Methyl-5-indolyl)-N'-(4-isoquinolyl) urea,
25 or a pharmaceutically acceptable salt thereof.
8. A compound according to any one of claims 1 to 7 for use in
therapy.
- 30 9. A pharmaceutical composition which comprises a compound according to any one of claims 1-7 and a pharmaceutically acceptable carrier or excipient.
- 35 10. A process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof, which process comprises:

-32-

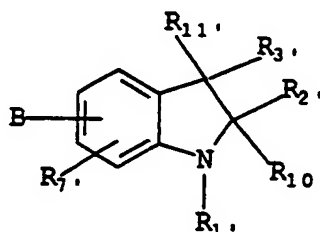
(a) the coupling of a compound of formula (II);



5

(II)

with a compound of formula (III);



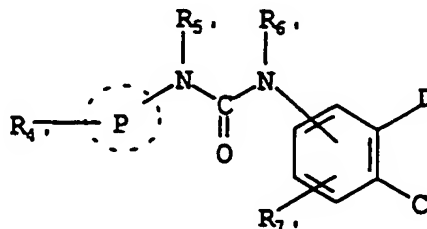
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(III)

wherein B is attached at the 4-, 5- or 6-position of the indole or indoline ring and A and B contain the appropriate functional group(s) necessary to form the moiety $-NR_5'CONR_6'$ when coupled, wherein R_5' and R_6' are R_5 and R_6 as defined in formula (I) or groups convertible thereto, and the variables R_1' , R_2' , R_3' , R_{10}' , R_{11}' , R_4' and R_7' are R_1 , R_2 , R_3 , R_{10} , R_{11} , R_4 and R_7 respectively, as defined in formula (I), or groups convertible thereto, and thereafter optionally and as necessary and in any appropriate order, converting any R_1' , R_2' , R_3' , R_{10}' , R_{11}' , R_4' , R_5' , R_6' and R_7' when other than R_1 , R_2 , R_3 , R_{10} , R_{11} , R_4 , R_5 , R_6 and R_7 respectively to R_1 , R_2 , R_3 , R_{10} , R_{11} , R_4 , R_5 , R_6 and R_7 , interconverting R_1 , R_2 , R_3 , R_{10} , R_{11} , R_4 , R_5 , R_6 and R_7 , and forming a pharmaceutically acceptable salt thereof; or

25

(b) cyclising a compound of formula (IV):



30

(IV)

wherein R₄' , R₅' , R₆' and R₇' are as defined in formulae (II) and (III) and C and D contain the appropriate functional group(s) necessary to form the indole or indoline ring substituted by R₁' , R₂' , R₃' , R₁₀' , and R₁₁' as

5 defined in formula (III), and thereafter optionally and as necessary in any appropriate order, converting any R₁' , R₂' , R₃' , R₁₀' , R₁₁' , R₄' , R₅' , R₆' and R₇' when other than R₁ , R₂ , R₃ , R₁₀ , R₁₁ , R₄ , R₅ , R₆ and R₇ , to R₁ , R₂ , R₃ , R₁₀ , R₁₁ , R₄ , R₅ , R₆ and R₇ , interconverting R₁ , R₂ , R₃ , R₁₀ , R₁₁ , R₄ , R₅ , R₆ and R₇ , and optionally thereafter forming a

10 pharmaceutically acceptable salt.

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC Int.Cl. 5 C07D403/12; A61K31/40; C07D417/12; C07D413/12 C07D401/12		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
Int.Cl. 5	C07D	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹		
Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
A	JOURNAL OF MEDICINAL CHEMISTRY. vol. 29, 1986, WASHINGTON US pages 2415 - 2418 P. FLUDZINSKI ET AL. '2,3-Dialkyl(dimethylamino)indoles: interaction with 5HT ₁ , 5HT ₂ , and rat stomach fundal seretonin receptors' cited in the application * page 2415-16 *	1,8,9
P,X	--- WO,A,9 205 170 (BEECHAM GROUP PLC) 2 April 1992 * complete document * -----	1,8,9
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>¹⁰ Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"A" document member of the same patent family</p> </div> </div>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search		Date of Mailing of this International Search Report
14 MAY 1993		11. 06. 93
International Searching Authority		Signature of Authorized Officer
EUROPEAN PATENT OFFICE		VAN BIJLEN H.

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SA 70896

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WO-A-9205170	02-04-92	AU-A- 8503891	15-04-92
